Efficacy of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration of Hilar Lymph Nodes for Diagnosing and Staging Cancer

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Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is used mostly in patients with non-small cell lung cancer (NSCLC) to sample mediastinal lymph nodes that are visible on computed tomography (CT). We sought to determine the efficacy of EBUS-TBNA in sampling enlarged hilar lymph nodes in this patient population.

Methods: From January 2004 to May 2007, patients with suspected NSCLC and CT or positron emission tomography (PET) imaging demonstrating enlarged (>1 cm) or PET-positive hilar lymph nodes underwent EBUS-TBNA. Patients with enlarged central mediastinal nodes were excluded. Identifiable lymph nodes at locations 10R, 10L, 11R, and 11L were aspirated. All patients underwent subsequent surgical staging or clinical follow-up as indicated. Diagnoses based on aspirates were compared with those based on surgical or clinical results.

Results: Of 213 patients evaluated (mean age, 56 years; 138 men), 188 (mean age, 56.3 years; 120 men) were diagnosed with NSCLC and were analyzed. In these patients, 229 lymph nodes, ranging 8 to 20 mm, were detected, and all were sampled. Of the 188 patients, 25 had a single enlarged node in a contralateral hilar position (N3), 40 had multiple enlarged ipsilateral nodes in the N1 position, and 123 had an ipsilateral single enlarged node in the N1 position. Overall, diagnostic sensitivity of EBUS-TBNA was 91%, specificity was 100%, and the positive predictive value was 92.4%. In the 25 patients with contralateral hilar nodes, sensitivity was 66%, specificity was 100%, and the positive predictive value was 96%.

Conclusions: No complications occurred. In experienced hands, EBUS-TBNA of enlarged hilar lymph visible on CT or hilar nodes that are PET scan-positive can provide diagnostic results similar to those for central mediastinal nodes.

Key Words: Endobronchial ultrasound, Lung cancer, Mediastinal lymphadenopathy, Hilar staging, Transbronchial needle aspiration.

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Correct staging of patients with non-small cell lung cancer (NSCLC) provides accurate information on the extent of disease and guides the choice of treatment. It is also fundamental for estimating prognosis and for comparing studies of treatments and survival. When there are no distant metastases, mediastinal lymph node involvement is the most important prognostic factor in patients with NSCLC, and the nature of this involvement influences therapeutic strategies.[1,2]

Since the tumor, node, metastasis lung cancer staging system was developed in 1968,[3] lymph node involvement has been categorized as N0 (no nodes involved), N1 (peribronchial, interlobar, or perihilar lymph nodes involved), N2 (ipsilateral mediastinal nodes involved), or N3 (contralateral mediastinal or supraclavicular nodes involved). The classification of these N descriptors into the overall tumor stages of I to III has been used to predict outcomes and to assist in treatment selection.[4]

The most recent report of the International Association for the Study of Lung Cancer analyzed more than 67,000 patients. In the report, among patients undergoing resection without induction therapy, Rusch et al.[5] identified three distinct prognostic groups: (1) patients with a single node in zone N1, (2) patients with multiple nodes in zone N1 or with a single node in zone N2, and (3) patients with multiple nodes in zone N2. Therefore, not only is the staging of central mediastinal lymph nodes important, but also the proper assessment of nodes in the hilar region before making definitive therapeutic decisions.

Hilar lymph nodes can be staged with noninvasive (e.g., imaging) and invasive (sampling) procedures. Computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET), and PET-CT are used for noninvasive imaging.[6–9] Despite advances in the latest imaging techniques and although they can identify nodes suspicious for malignancy, they provide only a clinical stage or diagnosis; invasive procedures and cytologic or histologic confirmation of

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biopsy samples (invasive staging) is still required to clarify the pathologic stage.[1–11]

Invasive staging of the hilar regions can be performed by video-assisted thoracoscopic surgery or open surgery.[10] Invasive staging can also be performed with needle biopsy techniques including transbronchial needle aspiration (TBNA), endoscopic ultrasound-guided fine-needle aspiration, and, most recently, endobronchial ultrasound-guided (EBUS-TBNA).[12]

Because of the anatomic location of hilar nodes, a reliable bronchoscopic staging approach may be superior in ease and complication rate when compared with other modalities.

The aim of this study was to evaluate the value of EBUS-TBNA in obtaining samples for staging hilar lymph nodes ipsilateral and contralateral to the primary lesion.

PATIENTS AND METHODS

Approval from the local institutional review board was obtained. From January 2004 to May 2007, all patients with lung masses suspicious for NSCLC and lymphadenopathy limited to a hilum were evaluated for inclusion in this prosepective study. All patients were presented in multidisciplinary Tumor boards, and a chest radiograph and CT scan of the chest (plain and contrast enhanced) were performed in all patients; PET scans were obtained on an individual basis based on clinical assessment. Patients with mediastinal lymphadenopathy or extrathoracic disease were excluded from the study, as well as the patients with comorbidities which did not allow for safe bronchoscopy. Written informed consent was obtained from all patients included in the study.

If the patient had never undergone bronchoscopy, conventional flexible bronchoscopy (model BF-160/T-180 bronchoscope; Olympus Ltd, Tokyo, Japan) was first performed to examine the tracheobronchial tree, followed by an EBUS examination with a dedicated EBUS-TBNA bronchoscope (model BF-UC260F-OL8; Olympus). If the patient had already undergone videobronchoscopy, the EBUS examination was performed directly. Bronchoscopy procedures were performed with the patient receiving local anesthesia and moderate sedation (midazolam) or general anesthesia.

Transbronchial Needle Aspiration

The EBUS-TBNA examination was performed with a flexible ultrasonic puncture bronchoscope with a linear scanning transducer according to a standard protocol as described previously and as an outpatient procedure.[12,13] The ultrasound transducer scans parallel to the insertion direction of the bronchoscope and is connected to a dedicated ultrasound scanner (EU-C60; Olympus Ltd, or Prosound alpha 5, Aloka, Japan) with Doppler-flow imaging to detect blood vessels.

The endoscope was passed through the mouth and vocal cords to the main carina, then to the distal left and right bronchi. Regional hilar lymph node stations (stations 10 and 11) were imaged systematically during slow withdrawal and rotation of the transducer (Figures 1, 2). Enlarged nodes were aspirated twice (Figure 3). Rapid on-site pathologic evaluation was not used. The aspirates were placed onto at least four glass slides, air dried, treated with Papanicolaou stain, and assessed by a cytopathologist.

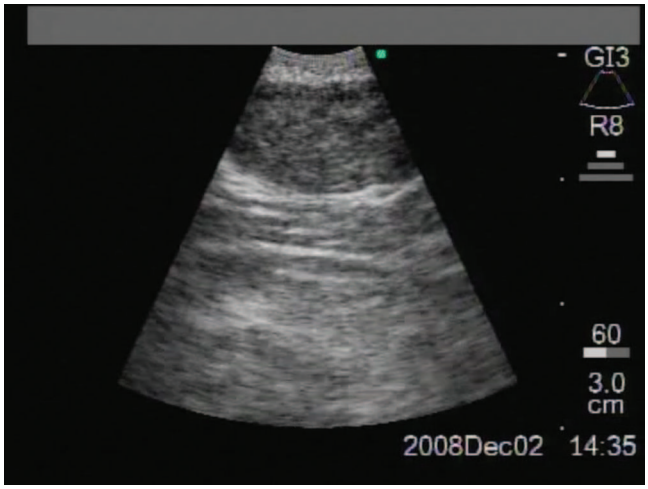

FIGURE 1. Single lymph node in the 11L position.

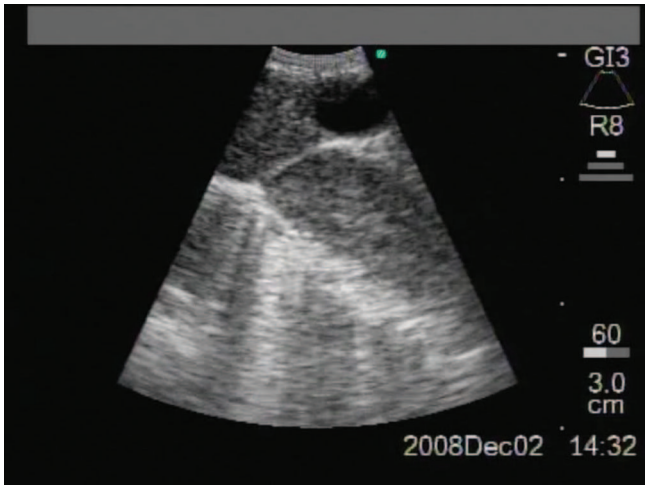

FIGURE 2. Two lymph nodes in the 11R position. The lymph node capsule are clearly visible because it is a small vessel.

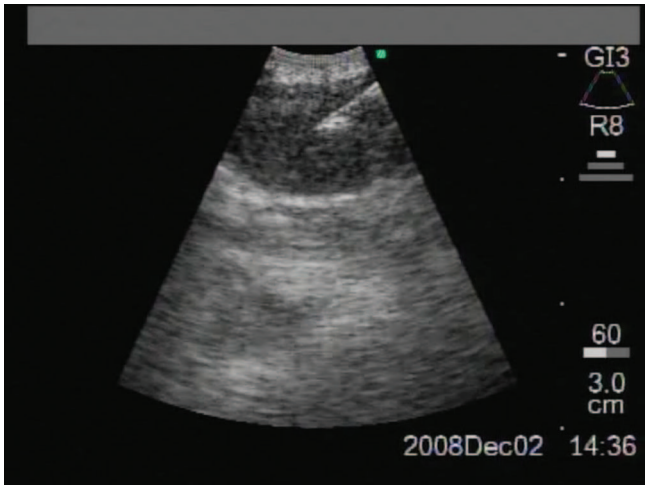

FIGURE 3. Needle entry into a single lymph node in the 11L position.

Establishing the Reference Diagnoses

The definitive diagnosis was made by biopsy of the primary parenchymal tumor and, the final pathologic staging was determined during subsequent thoracotomy, thoracoscopy, or during clinical follow-up for 6 months. Diagnoses based on real-time EBUS-TBNA were compared with those based on open thoracotomy, thoracoscopy, or clinical follow-up. A positive cytologic result of malignancy was accepted as evidence of cancer, and the patients were treated accordingly.

Statistical Methods

Diagnostic sensitivity, specificity, and accuracy were calculated using the standard definitions. Alpha was set at 0.05, and the SPSS 11.5 (SPSS Inc., Chicago, IL) statistical software package was used for all analyses.

RESULTS

From January 2004 to May 2007, 213 patients (mean age, 56 years; 138 men) were identified as having parenchymal lesions highly suspicious for NSCLC and enlarged or PET-positive hilar nodes only. A positive diagnosis of NSCLC based on open thoracotomy, thoracoscopy, or clinical follow-up was established in 188 patients (mean age, 56.3 years; 120 men). Of the 25 patients with other diagnoses, 12 had small cell lung cancer, five had sarcoidosis, and two of each had tuberculosis, cryptogenic organizing pneumonia, or distant metastasis (Table 1). Two patients refused surgery. Moderate sedation was used for the procedure in 133 patients (90 men) and general anesthesia in 55 patients (30 men). In the analyzed 188 patients, samples were obtained from all 229 identified enlarged or PET-positive lymph nodes (range, 8–20 mm; median, 15.6 mm; interquartile range, 0.36). The locations of these nodes were as follows: 25 patients (13%) had a single enlarged node in a contralateral hilar position of which 12 were PET positive. Forty (21%) had multiple enlarged nodes in the N1 position, and 123 (66%) had a single enlarged node in the N1 position.

Of the 163 patients with nodes in the ipsilateral hilar position, 123 had a single enlarged station, and 40 had two enlarged N1 station (e.g., 10R and 11R). Malignancy was confirmed to be present in 117 patients.

In the 25 patients with enlarged nodes in the contralateral hilar position 3 (12%) proved to be malignant.

Cancer was staged correctly by EBUS-TBNA in 174 of the 188 patients (93%). Surgery or clinical follow-up identified lymph node metastasis in the remaining 14 patients: 11 had a single ipsilateral node, two had two ipsilateral nodes, and one had a contralateral hilar node. Possible reasons for unsuccessful endobronchial staging in these patients include the lack of lymphocytes in the aspirate (seven patients), too much blood in the aspirate for analysis (four cases), and not sampling the correct node (two patients). The reason is unknown in one patient.

Endoscopic staging was correct in 112 of 123 patients (91%) with a single hilar node, in 38 of 40 patients (95%) with a double ipsilateral nodes, and in 24 of 25 patients (96%) with a contralateral hilar node.

Overall, sensitivity was 91%, specificity was 100%, and the positive predictive value was 92.4%. For the 25 patients with contralateral hilar nodes, sensitivity was 66%, specificity 100%, and positive predictive value was 96%. Patients with single or double hilar nodes did not differ significantly ($p = 0.7$).

No complications occurred during any procedure.

TABLE 1. Reasons of Exclusion of the Final Analysis (25 of 213 Patients) Based on the Final Diagnosis

Small cell lung cancer	12
Sarcoidosis	5
Tuberculosis	2
Crytogenic organising pneumonia	2
Refused surgery	2
Distant metastasis	2

DISCUSSION

In this trial, we showed that EBUS-TBNA performed very well when used to biopsy enlarged or PET-positive hilar lymph nodes and that it identified malignant hilar lymph nodes with the same accuracy as it detects malignant central mediastinal nodes. The 91% sensitivity, 100% specificity, and 92.4% positive predictive value are virtually the same performance characteristics as reported for mediastinal nodes.[12–16] In a recent multicenter study, we reported on the effectiveness and accuracy of EBUS-TBNA for evaluating mediastinal lymph nodes.[13] In 502 patients, 572 lymph nodes were punctured using EBUS-TBNA resulting in a confirmed diagnoses for 535 lymph nodes (94%). The sensitivity was 94%, and the specificity was 100%.

In an International Association for the Study of Lung Cancer study of more than 67,000 patients,[17] Rusch et al.[5] reported that survival varied by the number of involved nodal zones. Patients with a single N1 node had significantly better survival than did those with either multiple N1 nodes or single N2 node, and multiple N2 nodes were associated with a distinctly worse prognosis. These findings suggest that prognosis is affected by disease burden as well as by the anatomic location of involved lymph nodes.

These findings imply that proper anatomic staging of regional hilar nodes may be more important than assumed and that trials evaluating different therapeutic strategies for these patients may be warranted. If more detailed hilar evaluation will be required more often, then EBUS-TBNA is ideally suited for that task. Surgical approaches usually require video-assisted thoracoscopic surgery or thoracotomy and are reasonable for patients undergoing pulmonary resection, but obviously would play a lesser role for preresection staging. Endoscopic ultrasound-guided fine-needle aspiration although of excellent utility for central nodes does not reliably reach hilar nodal stages. EBUS-TBNA is a minimally invasive procedure that affords excellent access to the hilar stations and in this trial, we could show that, it has excellent performance characteristics not only in just identifying malignant involvement but also in the differentiation of the number of affected lymph node stations.

Limitations of the Study

EBUS-TBNA is an operator-dependent technique. All procedures in this study were performed by experienced bronchoscopists skilled in using EBUS. Further studies with more operators and centers will be necessary to establish the usefulness of the technique in routine practice.

CONCLUSIONS

In experienced hands, EBUS-TBNA of enlarged hilar lymph visible on CT or PET scans can provide diagnostic results similar to those for central mediastinal nodes.

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